REMARKS

Claim Amendments

Claim 1 has been amended to recite that the method of administering lives cells to a patient comprises injecting into a treatment site without open surgery to expose the treatment site. Claim 1 has been also been amended to recite that the microparticles of the administered composition are injected in an amount sufficient to provide a retention or growth surface for the cells to thereby provide a therapeutic effect in the patient.

Support for the amendment of Claim 1 can be found in the Specification at page 4, lines 18-20 and page 6, lines 7-10.

Rejections of Claims 1-5 and 13-22 Under 35 U.S.C. § 102(b) or (e)

The Examiner has rejected Claims 1-5 and 13-22 under 35 U.S.C. 102(b) or (e) as being anticipated by WO 96/18411 (Mooney '411) or U.S. Patent 6,281,015 (Mooney '015). The references will be collectively referred to herein as Mooney *et al.* in view of the relationship of the references. The Examiner stated that Mooney *et al.* disclose administering to a patient microspheres containing bioactive factors such as growth and/or angiogenic factors and cells that form cartilage. The Examiner then concluded that the method of Mooney *et al.* and Applicants' claimed method are the same. Applicants respectfully disagree.

As a preliminary matter, reference to specific teachings of Mooney *et al.* will refer to Mooney '411.

As currently claimed, the present invention is directed to a method of administering live cells to a patient comprising injecting into a treatment site of the patient, without open surgery to expose the treatment site, an effective amount of a composition comprising microparticles and live cells. The microparticles are injected in an amount sufficient to provide a retention or growth surface for the live cells to thereby provide a therapeutic effect in the patient. Advantageously, the composition comprising the microparticles and live cells permits the administration to be by injection which obviates the need for an open surgical intervention, as is necessary when the cells are implanted using, for example, polymer sponges. This feature is recited in the claims as amended.

Mooney *et al.* teach a method of enhancing survival, growth and differentiation of transplanted cells, in particular, hepatocytes. The enhancement it taught to result from the administration of polymer microspheres having growth factors incorporated therein to the same site as the transplanted cells. Mooney *et al.* teach that the transplanted cells are administered using two types of polymer matrices. Specifically, Mooney *et al.* teach the use of an implantable fibrous structure, such as the sponge of Example 3 (page 34, lines 19-22) and discussed at page 26, lines 16-20, or a hydrogel polymer solution as matrices for generating new tissue.

Notably, Mooney *et al.* do not teach or suggest the use of microparticles as a matrix to provide the microenvironment necessary for transplanted cells to be retained or grow and provide a therapeutic effect. In other words, although Mooney *et al.* administer microparticles containing growth factor, a secondary and distinct polymer matrix, which is not a microparticle, but rather a fibrous structure or hydrogel polymer solution, is always present to provide a suitable surface area for cell growth and tissue generation.

More specifically, Mooney *et al.* teach that when an implantable fibrous structure is used as the scaffolding for cell growth and tissue generation, the fibrous structure must be large enough to provide a surface area to allow adequate diffusion of nutrients and growth factors to the cells (page 25, line 28-page 26, line 3). The fibrous structures taught by Mooney *et al.* have sufficient interstitial spacing to allow cells to attach to the structure. Typically, the interstitial spacings are in the range of 100 to 300 microns, thereby requiring implantation in the patient. The use of an implantable fibrous structure as a scaffold for cell growth and tissue regeneration as taught by Mooney *et al.*, is not Applicants' claimed invention which uses microparticles as the surface to provide retention or growth of the administered cells and which administers the microparticles without open surgery to expose the treatment site.

The other matrix which Mooney *et al.* teach as suitable for generating new tissue results from administration of a hydrogel polymer solution. The hydrogel polymer solution hardens *in vivo* following administration due to the presence of physiological concentrations of calcium. Mooney *et al.* teach that the transplanted cells can be mixed with the hydrogel solution to form a suspension and then administered to the patient, wherein the hydrogel hardens providing a matrix for the cells to grow. However, administration of a solution of polymer having cells suspended

therein is not the administration of microparticles in a sufficient amount to provide a surface for the retention or growth of the administered cells, as claimed by Applicants.

Furthermore, it is known in the art that controlled delivery and containment of a liquid hydrogel system within a particular area is difficult and the liquid can spread to areas other than the implant site prior to solidification. The problem of containment prior to solidification is overcome by practicing Applicants' claimed invention utilizing microparticles as the surface for retention or growth of the administered cells. Certainly, this is neither taught or appreciated by Mooney *et al.*

As such, Mooney *et al.* teach a method of tissue generation which relies on the use of fibrous polymer structures (sponges) or liquid hydrogel to provide the surface for the cells to grow and generate new tissue *in vivo*. Applicants' claimed use of microparticles as a retention or growth surface for the adminstered cells is neither taught nor suggested by Mooney *et al.* In fact, one of skill in the art upon reading Mooney *et al.* would be taught that microparticles are an insufficient scaffold for cell growth and new tissue generation, since the bioactive containing microparticles of the Mooney *et al.* composition are always administered with a secondary and distinct from of polymeric matrix (e.g., a fibrous structure or hydrogel solution) to support cell growth. Therefore, Mooney *et al.* do not teach Applicants' claimed invention of administering live cells to a patient without open surgery to expose the treatment area and in an amount sufficient to provide a retention or growth surface for the administered cells.

In view of the above, Applicants' claims, particularly as amended, meet the requirements of 35 U.S.C. 102(b) and 102(e) and are patentable over the teachings of Mooney *et al.* Reconsideration and withdrawal of the pending rejection is respectfully requested.

Rejection of Claim 6 Under 35 U.S.C. § 103(a)

The Examiner has rejected Claim 6 under 35 U.S.C. § 103(a) over Mooney *et al.* (discussed above) in view of Purchio *et al.* (U.S. Patent No. 5,902,741). The Examiner is relying on Purchio *et al.* for its teaching of articular cartilage. The deficiencies of Mooney *et al.*, however, are far greater than the lack of a specific teaching of articular cartilage and are not cured by Purchio *et al.*

Mooney *et al.* is discussed in detail above. Briefly, Mooney *et al.* teach a method of enhancing survival, growth and differentiation of transplanted cells by administering bioactive-containing microspheres to the same site as transplanted cells. Mooney *et al.* do not teach or suggest the use of microparticles as a matrix to provide the microenvironment necessary for transplanted cells to be retained or grow and provide a therapeutic effect. In fact, even though microparticles containing growth factor are administered in accordance with Mooney *et al.*, a secondary and distinct polymer matrix is always present to provide a suitable surface area for cell growth and tissue generation. As such, one of ordinary skill in the art upon reading Mooney *et al.* would not be motivated to use microparticles to support retention and growth of the administered cells, as Applicants have done, with any reasonable expectation of success, since Mooney *et al.* teach that a secondary polymer matrix, distinct from the micropshere matrix used to deliver the growth factor, is needed. Absent this teaching or suggestion, Mooney *et al.* can neither anticipate nor make obvious Applicants' claimed invention.

Purchio *et al.* teach a method for the *in vitro* growth and preparation of cartilage, which can then be used *in vivo*. The method involves the growth of stromal cells (e.g., cartilage cells) on a three dimensional framework. The three dimensional framework should be of a appropriate size to allow the stromal cells to stretch across the openings of the framework. Openings in the framework can range from about 150 μm to about 220 μm. Purchio *et al.* do not teach or suggest the use of microparticles to provide a surface for the retention and growth of live cells following *in vivo* administration. Therefore, the teachings of Purchio *et al.* do not cure the deficiencies of Mooney *et al.*, as discussed above.

In conclusion, Mooney *et al.* does not teach the use of microparticles as a retention and growth surface for live cells following administration *in vivo*. In fact, Mooney *et al.* teach that a matrix, distinct from microspheres is needed to provide a surface for cell growth. Purchio *et al.* also do not teach the use of microparticles as a retention and growth surface for live cells. Applicants' claims recite that the microparticles of the administered composition provide a retention and growth surface for the live cells of the composition. As such, neither reference alone nor in combination makes obvious Applicants' claimed invention.

In view of the above, the claims, particularly as amended, meet the requirements of 35 U.S.C. § 103(a) and are patentable over the teachings of Mooney *et al.* alone or in combination

with Purchio *et al.* Reconsideration and withdrawal of the pending rejection is respectfully requested.

Rejection of Claim 7-12 Under 35 U.S.C. § 103(a)

The Examiner has rejected Claims 7-12 under 35 U.S.C. § 103(a) over Mooney *et al.* (discussed above) in view of Holland *et al.* (U.S. Patent No. 5,550,050). In particular, the Examiner stated that it would have been obvious to include the secretory cells of Holland *et al.* as the cells implanted by Mooney *et al.* It appears that the Examiner in relying on Holland *et al.* for its teaching of secretory cells. The deficiencies of Mooney *et al.*, however, go far beyond the lack of a specific teaching of secretory cells as the type of cells administered, and are not cured by Holland *et al.*

Mooney *et al.* is discussed in detail above. Briefly, Mooney *et al.* teach a method of enhancing survival, growth and differentiation of transplanted cells by administering bioactive-containing microspheres to the same site as transplanted cells. Mooney *et al.* do not teach or suggest the use of microparticles as a matrix to provide the microenvironment necessary for transplanted cells to be retained or grow and provide a therapeutic effect. In fact, even though microparticles containing growth factor are administered in accordance with Mooney *et al.*, a secondary and distinct polymer matrix is always present to provide a suitable surface area for cell growth and tissue generation. As such, one of ordinary skill in the art upon reading Mooney *et al.* would not be motivated to use microparticles to support retention and growth of the administered cells, as Applicants have done, with any reasonable expectation of success, since Mooney *et al.* teach that a secondary polymer matrix, distinct from the micropshere matrix used to deliver the growth factor, is needed. Absent this teaching Mooney *et al.* can neither anticipate nor make obvious Applicants' claimed invention.

Holland *et al.* teach that secretory cells (e.g., PC-12 cells) can be placed inside a semipermeable jacket, sealed by knotting or crimping, for example, and implanted at a desired site. The semipermeable jacket permits diffusion of cell secretions through the jacket. Holland *et al.* do not teach or suggest the use of microparticles to provide a surface for the retention and growth of live cells following *in vivo* administration. Therefore, the teachings of Holland *et al.* do not cure the deficiencies of Mooney *et al.*, as discussed above.

In conclusion, Mooney *et al.* does not teach the use of microparticles as a retention and growth surface for live cells following administration *in vivo*. In fact, although Mooney *et al.* actually use microspheres for delivery of bioactive, a different form of matrix is selected to support cell growth. Holland *et al.* also does not teach the use of microparticles as a retention and growth surface for live cells. Applicants' claims recite that the microparticles of the administered composition provide a retention and growth surface for the live cells of the composition. As such, neither reference alone nor in combination makes obvious Applicants' claimed invention.

In view of the above, the claims, particularly as amended, meet the requirements of 35 U.S.C. § 103(a) and are patentable over the teachings of Mooney *et al.* alone or in combination with Holland *et al.* Reconsideration and withdrawal of the pending rejection is respectfully requested.

Rejection of Claims 1-5 and 13-22 Under 35 U.S.C. § 103(a)

The Examiner has rejected Claims 1-5 and 13-22 under 35 U.S.C. § 103(a) as unpatentable over Mooney *et al.* in view of U.S. Patent No. 5,830,507 (Armstrong) and 5,980,888 (Dimoudis *et al.*). In particular, the Examiner stated that it would have been obvious to omit the polymer matrix or solution of Mooney *et al.* and attach the cells to grow on microspheres and produce tissue as suggested by Armstrong and Dimoudis *et al.* Applicants respectfully disagree.

As a preliminary matter, it appears that the Examiner is asserting that Mooney *et al.* lack a teaching of the use of microspheres as a surface to grow cells and is relying on Armstrong and Dimoudis *et al.* for this teaching. If, in fact, this is the Examiner's understanding of Mooney *et al.*, then the rejection under 35 U.S.C. 102(b) and (e) should be withdrawn in view of Applicants' amended claims which recite that the microparticles provide a retention or growth surface for the administered cells to thereby provide a therapeutic effect.

The presently claimed invention is directed to a method of administering live cells to a patient comprising injecting into a treatment site of the patient, without open surgery to expose the treatment site, an effective amount of a composition comprising microparticles and live cells. The microparticles are injected in an amount sufficient to provide a retention or growth surface

for the live cells to thereby provide a therapeutic effect in the patient. Advantageously, the composition comprising the microparticles and live cells permits the administration to be by injection which obviates the need for an open surgical intervention, as is necessary when the cells are implanted using, for example, polymer sponges. This feature is recited in the claims as amended.

Mooney *et al.* teach a method of enhancing survival, growth and differentiation of transplanted cells by administering bioactive-containing microspheres to the same site as transplanted cells. Mooney *et al.* do not teach or suggest the use of microparticles as a matrix to provide the microenvironment necessary for transplanted cells to be retained or grow and provide a therapeutic effect. In fact, even though microparticles containing growth factor are administered in accordance with Mooney *et al.*, a secondary and distinct polymer matrix is always present to provide a suitable surface area for cell growth and tissue generation. As such, one of ordinary skill in the art upon reading Mooney *et al.* would not be motivated to use microparticles to support retention and growth of the administered cells, as Applicants have done, with any reasonable expectation of success, since Mooney *et al.* teach that a secondary polymer matrix, distinct from the micropshere matrix used to deliver the growth factor, is needed.

The secondary references (Armstrong and Dimoudis *et al.*) do not cure the deficiencies of Mooney *et al.* More specifically, Armstrong teach the use of a slurry of microspheres which are coated with skin cells for application to the surface of a burn or wound. The slurry of skin cell-coated microspheres are applied to the skin injury as would be a salve or paste. As such, there is no teaching or suggestion in Armstrong of injecting the skin cell-coated microspheres into a treatment site without open surgery to expose the treatment site since the treatment site is an exposed skin surface which has been damaged (e.g, burned or wounded). Further, the advantages of using the microparticles and the problems solved by the use of microparticles, as taught by Armstrong, are specific to the use of skin cells for exposed skin surface application not for injection into a treatment site without opent surgery to expose the treatment site. For example, Armstrong teaches that the microsphere slurry, in view of its paste-like consistency, can correct for contour variations present in the wound upon application to the surface (Col. 7, lines 53-54). In addition, the skin cell-coated microsphere slurry can be delivered to the entire surface of the

wound avoiding non-contact areas encountered with the use of meshes (Col. 7, lines 50-53). Moreover, Mooney *et al.* actually use micropsheres for delivery of bioactive, but select a different form of matrix to support cell growth. As such, one of ordinary skill in the art would not be motivated to substitute the microspheres of Armstrong for the implantable fibrous structures of Mooney *et al.*, in view of the teaching of Mooney *et al.* that the fibrous structures (in addition to microspheres) are needed to support growth of cells following implantation and the absence of a teaching in Armstrong of injection of microparticles to a treatment site to exert a therapeutic effect internally.

Dimoudis *et al.* add little to the teachings of Armstrong. More specifically, Dimoudis *et al.* teach microcarriers having epithelial cells attached thereto for the treatment of skin wounds. The microcarriers having the attached epithelial cells are applied directly, for example, spread over the surface of the skin wound (Col. 5, lines 19-20 and Col. 6, line 45). There is no teaching or suggestion that the microcarriers be injected into a treatment site without open surgery to expose the treatment site, as the site is the surface of the skin which is readily accessible. In addition, the advantages of using the microcarriers are specific to the generation of skin tissue and surface application, not for injection into a treatment without open surgery to expose the treatment site. For example, Dimoudis *et al.* teach that the use of microcarriers with the epithelial cells avoids difficulties encountered with skin sheets and can provide non-differentiated keratinocytes capable of proliferation which are not readily provided using skin sheets. In view of the above, one of ordinary skill in the art would not be motivated to substitute the microcarriers of Dimoudis *et al.* for the implantable fibrous structures of Mooney *et al.*

Therefore, the claims, particularly as amended, meet the requirements of 35 U.S.C. §103(a) and are patentable over the teachings of Mooney *et al.* either alone or in combination with Armstrong and Dimoudis *et al.* Reconsideration and withdrawal of the pending rejection is respectfully requested.

Rejection of Claim 6 Under 35 U.S.C. § 103(a)

The Examiner has rejected Claim 6 under 35 U.S.C. § 103(a) as being unpatentable over Mooney *et al.* in view of Armstrong and Dimoudis *et al.* and further in view of Purchio *et al.* Applicants respectfully disagree.

Mooney *et al.* do not teach or suggest the use of microparticles as a matrix to provide the microenvironment necessary for administered cells to be retained or grow and provide a therapeutic effect. Rather, Mooney *et al.* teach that a matrix distinct from a microsphere matrix is necessary for administered cells to grow. Armstrong and Dimoudis *et al.* do not cure the deficiencies of Mooney *et al.* For example, Armstrong and Dimoudis *et al.* teach the use of microspheres coated with skin cells and microcarriers having epithelial cells attached. The compositions of Armstrong and Dimoudis *et al.* are for application to the skin surface, not for injection into a treatment site without open surgery to expose the treatment site. One of ordinary skill in the art upon reading Armstrong and Dimoudis *et al.* would not be motivated to substitute the microcarrier/cell mixture used for surface application for the transplanted matrix of Mooney *et al.*, particularly since Mooney *et al.* actually use microspheres for delivery of a bioactive agent, but select a different form of matrix for cell growth. The teaching of Purchio *et al.* that articular cartilage can be generated on three dimensional framework having openings ranging from 150 μm to about 220 μm does not cure the deficiencies of Mooney *et al.*, Armstrong and Dimoudis *et al.* either alone or in combination as discussed above.

Therefore, the claims, particularly as amended, meet the requirements of 35 U.S.C. §103(a) and are patentable over the teachings of Mooney *et al.* either alone or in combination with Armstrong and Dimoudis *et al.* and further in view of Purchio *et al.* Reconsideration and withdrawal of the pending rejection is respectfully requested.

Rejection of Claims 7-12 Under 35 U.S.C. § 103(a)

The Examiner has rejected Claims 7-12 under 35 U.S.C. § 103(a) as being unpatentable over Mooney *et al.* in view of Armstrong and Dimoudis *et al.* and further in view of Holland *et al.* Applicants respectfully disagree.

The teachings of Mooney *et al.*, Armstrong and Dimoudis *et al.* are discussed in detail immediately above. The teaching of Holland *et al.* that secretory cell(e.g., PC-12 cells) can be placed inside a semipermeable jacket, sealed by knotting or crimping, for example, and implanted at a desired site, does not cure the deficiencies of Mooney *et al.*, Armstrong and Dimoudis *et al.* either alone or in combination, as discussed above.

Therefore, the claims, particularly as amended, meet the requirements of 35 U.S.C. §103(a) and are patentable over the teachings of Mooney *et al.* either alone or in combination with Armstrong and Dimoudis *et al.* and further in view of Holland *et al.* Reconsideration and withdrawal of the pending rejection is respectfully requested.

Rejection of Claims 1-5 and 13-22 for Obviousness-Type Double Patenting

The Examiner has rejected Claims 1-5 and 14-22 for Obviousness-Type Double Patenting over Claims 1-12 of U.S. Patent No. 6,719,970. Applicants will consider filing a Terminal Disclaimer to overcome this rejection upon an indication of otherwise allowable subject matter.

Rejection of Claim 6 for Obviousness-Type Double Patenting

The Examiner has rejected Claim 6 for Obviousness-Type Double Patenting over Claims 1-12 of U.S. Patent No. 6,719,970 in view of Purchio *et al.* Applicants will consider filing a Terminal Disclaimer over U.S. Patent No. 6,719,970 to overcome this rejection upon an indication of otherwise allowable subject matter.

Rejection of Claim7-12 for Obviousness-Type Double Patenting

The Examiner has rejected Claims 7-12 for Obviousness-Type Double Patenting over Claims 1-12 of U.S. Patent No. 6,719,970 in view of Holland *et al.* Applicants will consider filing a Terminal Disclaimer over U.S. Patent No. 6,719,970 to overcome this rejection upon an indication of otherwise allowable subject matter.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

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